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# Accepted Manuscript

Clinical outcomes for patients with liver-limited metastatic colorectal cancer: Arguing the case for specialist hepatobiliary multidisciplinary assessment

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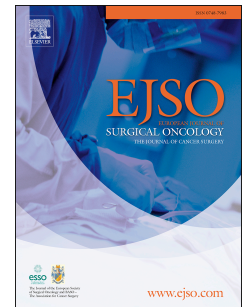
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**Title**

Clinical outcomes for patients with liver-limited metastatic colorectal cancer: Arguing the case for specialist hepatobiliary multidisciplinary assessment

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### Abstract

In patients with liver-limited metastatic colorectal cancer, hepatic resection can offer a significant survival benefit over systemic therapy alone. Specialist hepatobiliary multidisciplinary meetings are currently believed to provide the best forum to discuss the management for these patients.

A retrospective analysis was undertaken of patients diagnosed with liver-limited metastatic colorectal cancer over 6 months within a cancer network in the United Kingdom. In addition, patients who were diagnosed but not referred to the hepatobiliary meeting were discussed within a virtual multi-disciplinary setting. Contributors were blinded and proposed management recorded.

159 newly diagnosed patients with liver-limited metastatic colorectal cancer were identified. 68 (43%) were referred at initial diagnosis and 38 (24%) referred following systemic treatment. 35 (51%) who were discussed at baseline underwent a subsequent hepatectomy or radio frequency ablation, as did 18 (47%) patients referred after chemotherapy. Of the remaining 53 (33%) patients not referred, imaging was available for 31 (58%). Decisions regarding potential liver-directed therapy were discussed within a multi-disciplinary setting. 13 (41.9%) were identified as resectable or potentially resectable and 11 (35.5%) may have been suitable for a

clinical trial. In reality, none of these 31 patients (100%) underwent surgery or ablation.

Whilst the majority of patients with liver-limited metastatic colorectal cancer were referred appropriately, this study demonstrates that a significant number with potentially resectable disease are not being discussed at specialist meetings. A review of all diagnosed cases would ensure that an increased number of patients are offered hepatic resection or ablation.

### **Clinical outcomes for patients with liver-limited metastatic colorectal cancer: Arguing the case for specialist multidisciplinary assessment**

#### **Background**

Colorectal cancer (CRC) is the 3<sup>rd</sup> leading cause of cancer related mortality worldwide. Advances in systemic therapy have changed the treatment paradigm of stage IV disease and the median overall survival for metastatic CRC is now 26-30 months with 5 year survival rates of 11% [1-3]. Yet there is mounting evidence demonstrating improved outcomes in a select group of patients with resectable liver-limited metastases. R0 hepatic resections can lead to 5-year survival rates of 36-58% and 10 year figures can reach 17%-26%[4-6]. In CRC, the liver is often the initial site of metastatic spread due to direct invasion via the hepatic portal vein. 20% of patients with Stage IV disease present with CRC liver metastases (CLM) with a further 50% or more developing subsequent metachronous CLM. As several retrospective studies have now demonstrated significantly improved survival following hepatic metastasectomies, it is no longer justifiable to perform randomised trials comparing surgery with systemic treatment alone[5-7].

As expected, an R0 resection is required to achieve optimal survival and thus liver metastasectomy remains a highly skilled procedure. In the United Kingdom (UK) these operations are restricted to specialist hepato-biliary (HPB) units following discussion within a specialist HPB oncology multi-disciplinary meeting (MDM). Each MDM should include dedicated HPB surgeons, radiologists and oncologists. A proposed pan-European consensus suggested that MDM discussions should take place both at presentation and prior to subsequent major treatment decisions[8]. Current National Institute for Health Care and Excellence (NICE) guidelines state that if a computer tomography [9] scan of a patient with CRC shows metastases confined to the liver, a specialist HPB MDM should decide whether further imaging is needed to confirm whether surgery is possible for the patient (or potentially possible) after further treatment [10]. NICE guidance also states that local cancer networks should agree pre-determined criteria specifying which patients should be referred to the HPB MDM. However the definition of what constitutes resectable disease continues to evolve with advancing surgical and imaging techniques and therefore should only be determined by a specialist team. Historically, metastasectomies were reserved for patients with isolated liver lesions. Yet the combination of novel systemic therapies and more sophisticated surgical procedures mean resections can now be offered to patients with more extensive disease. Therefore many clinicians are now of the opinion that all patients with limited CLM should be referred for specialist HPB MDM review to avoid inappropriately denying patients surgery. Patients not suitable for hepatic resection, but with isolated liver metastases, should be enrolled in clinical trials where possible. Outcomes for loco-regional therapies such as microwave ablation (MA), radiofrequency ablation (RFA), irreversible electroporation or selective internal radiation therapy (SIRT) remain largely undetermined and prospective studies are required to evaluate

their benefit [11-14]. Results from a recently reported phase II study demonstrating improved overall survival in patients with up to 9 CLM treated with combined chemotherapy and RFA compared with chemotherapy alone suggests multi-modality treatment may be of benefit[15]. Further UK guidelines addressing the resection of CLM were proposed by a select panel including liver surgeons, gastroenterologists, oncologists, diagnostic and interventional radiologists and general surgeons in 2006. It stated that patients under consideration of loco-regional treatment to hepatic metastases should be discussed within a specialist HPB MDM. In addition, consideration of patients for resection of liver metastases should be carried out by a high volume centre and the decision regarding fitness for surgery should be undertaken by an anaesthetist and liver surgeon. Despite these guidelines, there appears to be significant discordance within referral practices to specialist HPB MDMs and the subsequent management of liver-limited disease. The rate of CLM resection has been shown to vary significantly across the UK [16].

We conducted a study that retrospectively assessed referral rates for patients with liver-limited metastatic CRC to the central HPB MDM over a 6-month period, within a large dedicated cancer network. Cases that had not been discussed were then referred for virtual HPB MDM discussions with MDM contributors blinded to assess potential disparity between referral rates and suitability for surgery, SIRT or inclusion within a clinical trial.

## **Methods**

A retrospective analysis was undertaken of all patients with liver-limited metastatic CRC across a 6-month period in 2012 within the South East London Cancer Network

(SELCN) and Kent and Medway Cancer Network (KMCN). The combined population served by these networks is approximately 2.9 million. All cases diagnosed with CRC within both networks during this time period were collated from local CRC MDM referral data. From these records, all patients with liver limited CRC were then identified. Using information from a prospectively maintained MDM database from the HPB centre, patients were categorised into three groups; Patients referred to the specialist HPB MDM at diagnosis, those only referred following initial treatment and those that were never referred. Each referring hospital had a local CRC MDM that included colorectal surgeons, medical and clinical oncologists and diagnostic radiologists. In these hospitals, one of the specialist HPB surgeons from the tertiary liver centre attended these CRC MDMs monthly. The centre specialist HPB MDT occurred twice weekly and was attended by HPB surgeons, interventional radiologists, colorectal surgeons, histopathologists and medical and clinical oncologists. Information regarding baseline demographics, performance status [17], disease distribution and management were collated.

For patients that had not been discussed within the specialist HPB MDM, a subsequent virtual MDM discussion with a liver surgeon, a dedicated liver radiologist and an oncologist was organised at the tertiary centre for all cases where imaging was available. Patients were discussed within 'real-life' MDMs and participating MDM contributors were blinded for each discussion. Proposed management was then compared with actual outcomes for each patient.

To compare categorical variables, the chi-squared test or the Fischer's exact test was used where appropriate. To compare continuous variables, the Mann-Whitney (two-tailed) test was used. Statistical analysis was performed using SPSS software package version 22.



## **Results**

159 patients with liver-limited metastatic colorectal cancer were identified. 68 patients (42.7%) were referred to the specialist HPB MDM at initial presentation of liver metastases, 38 patients (23.9%) were only referred following at least one course of systemic treatment and a further 53 patients (33.4%) were never referred to the HPB MDM. The median ages for patients referred at initial diagnosis, subsequent referrals and those not referred were 68.1, 65.1 and 69.9 respectively, without statistical difference between groups ( $p=0.23$ ) (see Table 1.). 119 patients (79.3%) presented with synchronous liver metastases, 31 patients (20.6%) with metachronous disease and timing of hepatic spread was unknown for the remaining 9 patients (see Figure 1.). 42.0% of patients with synchronous CLM were referred at initial diagnosis and 26.0% were only referred after systemic treatment. This was compared with 58.1% and 16.1% respectively for metachronous disease ( $P=0.11$ ).

Performance status [17] was available for 59 patients (37.0%) and was measured using the Eastern Cooperative Oncology Group Performance Status scale (ECOG PS). 52.5% of all patients referred at initial diagnosis had a PS of 0 or 1, and 6.0% had a PS of 2 or higher (PS was unknown for the remaining 41%) (Figure 2). For patients referred after initial treatment, 25% were 0-1 and 16% were 2 or higher. 22% of patients that were never referred had a good PS of 0 or 1, suggesting PS was not the reason for non-referral in this sub-group of patients where baseline fitness was known. Information regarding metastatic distribution was available for 140 (88%) patients. As expected, the majority of patients not referred to the MDM had multiple liver metastases. However 24% with a solitary liver lesion were never referred to the HPB MDM (figure 3). Similarly, 26% with solitary sites of disease were only referred after systemic

treatment. Amongst the 68 patients that were referred at initial presentation, surgery or RFA was offered to 35 (51.5%) and SIRT was offered to 2 patients (2.9%) within the FOXFIRE trial (an open-label phase III trial of chemotherapy with or without radioembolisation for liver-limited metastatic CRC) [18]. Amongst the 38 patients that were referred following initial treatment to the MDM, resection or RFA was offered to 18 patients (47.4%) and no patients were offered SIRT. Of patients that not discussed in the MDM, none had SIRT (Table 2). 81% of patients with liver metastases that were not referred to the specialist MDM were treated with systemic therapy including chemotherapy and antibody treatment.

Of the 53 patients that were not referred to the specialist MDM, imaging was available for 31 patients and these patients were discussed in a virtual MDM. 25 of these patients had synchronous liver metastases and 6 had metachronous liver disease following initial management of the CRC primary tumour. Extra-hepatic disease was identified on imaging for 3 patients. For those with liver-limited cancer, imaging suggested 13 patients (41.9%) had resectable or potentially resectable disease. A further 11(35.5%) patients were potentially eligible for the FOXFIRE trial. The MDM recommendation for 5 patients (16.1%) was palliative systemic therapy and for a further 2 (6.5%), proposed management was 'best supportive care' based on clinical information and imaging.

### **Discussion**

This study demonstrated that a third of patients with liver-limited metastatic CRC within a large cancer network were never referred to a specialist HPB MDM. The role of metastasectomy in CRC has become standard practice and in a select group of patients can achieve outcomes similar to those seen with stage III disease. Yet determining which patients fall in to this category requires specialist consideration. With an evolving

definition of what constitutes resectable disease, the decision to operate or not must be made within an HPB MDM in order to ensure that operable cases are not missed.

The reasons for non-referral are unknown and likely to be multi-factorial. One of the limitations to this study was that a complete medical history was not always available for each patient. It is possible that these patients may have had clear surgical contraindications or significant co-morbidities that may have rendered them unsuitable for resection. However the previously mentioned UK guidelines state that a liver surgeon and anaesthetist should determine surgical fitness. Dedicated HPB centres provide their own pre-assessment service designed to assess fitness depending on the procedure offered, as varying surgical and interventional techniques carry differing anaesthetic and surgical risk. Therefore to avoid discounting patients inappropriately, patients deemed unfit by referring hospitals still require specialist discussion. In addition 81% of all patients not referred, received systemic chemotherapy thereby confirming they had acceptable fitness for cytotoxic treatment.

Imaging was not available for 22 of the 53 patients that were not referred to the MDM. Therefore our figures may be under representative of the cases suitable for surgery or loco-regional therapies. A previous study conducted in the north of England in 2009 also found disparities in MDM referral rates[19]. Records of 631 patients with liver-limited CRC within a cancer network were reviewed. 29% of patients not referred due to perceived inoperability despite good PS, were subsequently deemed operable following retrospective review of imaging by liver specialists. A further 15.3% had equivocal imaging. A subsequent separate study published in 2012 evaluated outcomes for a similar cohort of patients from a prospectively maintained database[20]. 110 patients treated with palliative chemotherapy were identified over a 12-month period. 53 patients that had not been discussed within a specialist HPB MDM had liver-limited

disease. Imaging for these patients were then reviewed by six liver surgeons who were blinded to patient details. 33 patients (63%) had tumours that were considered potentially resectable with a high level of inter-observer agreement. Despite these previous studies, our findings demonstrate that there remains a clear disparity between patients referred to the HPB MDM and those that should have been referred in accordance with current guidelines. Even if surgery is not possible for patients with liver limited disease, their tumours may be amenable to alternate loco-regional therapy offered by specialist HPB teams. Although surgical techniques continue to improve and definitions of operability continue to be amended, not all patients with isolated liver disease are suitable for resection. For example, the number of liver metastases present has been found to be a predictor of poor survival [12, 21]. This emphasizes the importance of careful patient selection as even if disease can be resected, surgery may not impact outcome. Patients with limited liver metastases that are inoperable may benefit from loco-regional therapies but as there is limited prospective evidence for the survival benefits of such treatments, and as such these patients should be enrolled in clinical trials were available.

The liver is the most common site for metastasectomy in CRC. However, there is also a role for directed therapy to other sites such as RFA or surgery to small volume lung metastases or even peritoneal disease. Therefore in the era of pioneering imaging, surgical and ablative techniques, a diagnosis of metastatic CRC is no longer synonymous with incurable disease. This important paradigm shift necessitates careful multidisciplinary planning of these select patients. The current universally accepted staging classification, the American Joint Committee on Cancer (AJCC) stage, does not reflect the intricacies of oligometastatic disease. A more sophisticated staging system may help identify patients suitable for curative therapy. Whilst the current

recommendations are to discuss all patients with liver-limited metastatic CRC in a specialist HPB MDM, it may be that these patients require their own MDM rather than be discussed amongst primary HPB cancer cases. For example a specialist 'metastatic CRC MDM' including colorectal, hepatobiliary and thoracic teams as well as interventional radiologists and oncologists could help select patients with low-volume metastatic disease suitable for metastastectomies or loco-regional therapy.

Our study highlights the urgent need to improve referral practises to specialist HPB MDMs. Increased referrals are likely to equate to increased resection rates and subsequent improved survival for patients with liver-limited metastatic CRC.

#### Future Directions

In order to maintain uniformity of care in keeping with national guidance, all patients with oligometastatic CRC should be discussed within specialist MDM settings. For those with isolated CLM, images should be reviewed by hepatobiliary surgeons and radiologists to ensure surgery is offered where available. In cases where surgery is not possible, enrollment in clinical trials that include loco-regional therapies may be appropriate. For those with significant co-morbidities thought to be high risk, referral to tertiary liver centres should be made for assessment by a liver surgeon and anesthetist.

	Total (N)	Referred at first diagnosis	Referred but not at first diagnosis	Never referred
Age				

<b>Average (years)</b>	68.1	68.1 (31-100)	65.3 (34-81)	69.9 (40-90)
<b>31-40</b>	4	1	2	1
<b>41-50</b>	4	3	1	0
<b>51-60</b>	29	12	7	10
<b>61-70</b>	37	21	12	14
<b>71-80</b>	48	20	15	13
<b>81-90</b>	32	9	1	12
<b>91-100</b>	2	2	0	0
<b>Performance status</b>				
<b>0-1</b>	40	21 (52.5%)	10 (25.0%)	9 (22.5%)
<b>2-4</b>	19	6 (31.6%)	3 (15.7%)	10 (52.7%)
<b>Unknown</b>	100	41 (41.0%)	25 (25.0%)	34 (34.0%)
<b>Presentation of metastatic disease</b>				
<b>Synchronous</b>	119	50 (42.0%)	31 (26.0%)	38 (32.0%)
<b>Metachronous</b>	31	18 (58.1%)	5 (16.1%)	8 (25.8%)
<b>Number of metastatic sites</b>				
<b>1</b>	38	19 (50.0%)	10 (26.3%)	9 (23.7%)
<b>2-3</b>	36	21 (58.3%)	12 (33.0%)	3 (8.7%)
<b>4-6</b>	12	8 (61.5%)	3 (23.1%)	1(8%)
<b>Multiple</b>	54	19 (35.2%)	12 (22.2%)	23(42.6%)

Table 1. Patient demographics and disease distribution per referral group

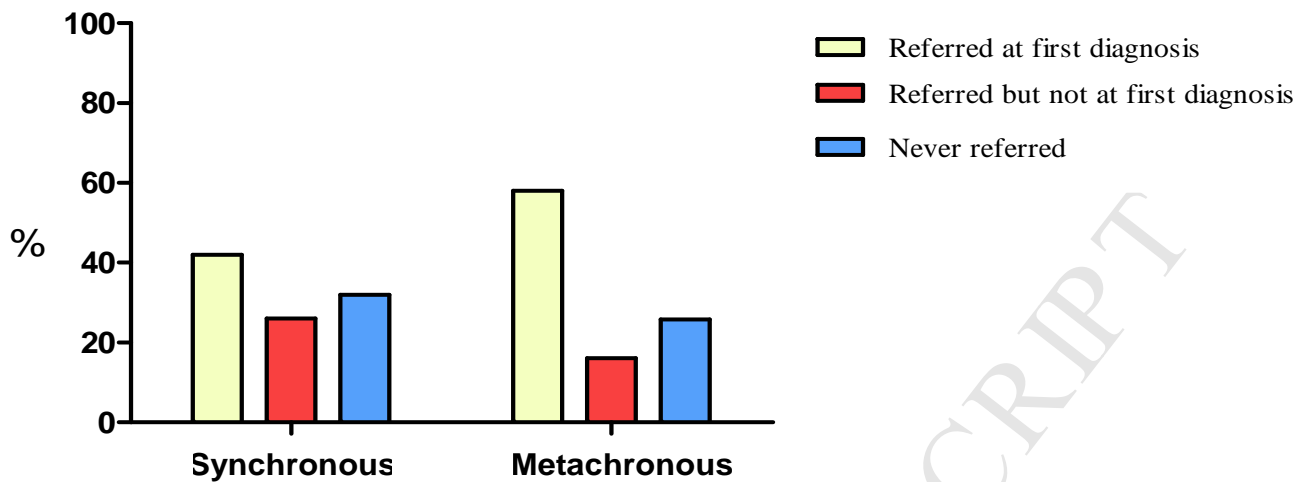


Figure 1. Percentage of patients with synchronous and metachronous metastases per referral group. Patients were more likely to be referred at initial presentation if they had metachronous disease.

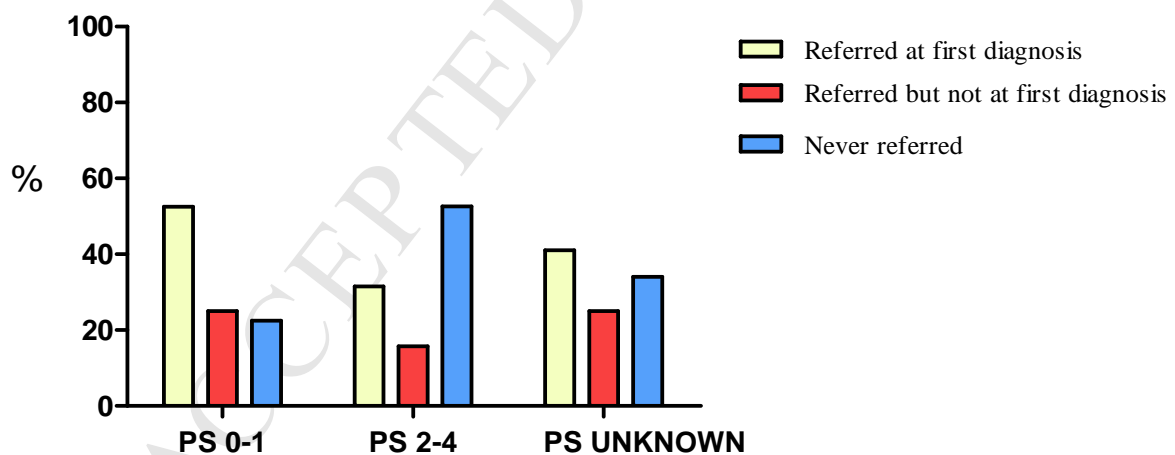


Figure 2. Eastern Cooperative Oncology Group Performance Status for patients at the time of diagnosis with liver metastases per referral group. More than 20% of patients with a good PS (0-1) were never referred to the HPB MDM. (PS=performance status, MDM=multi-disciplinary meeting).

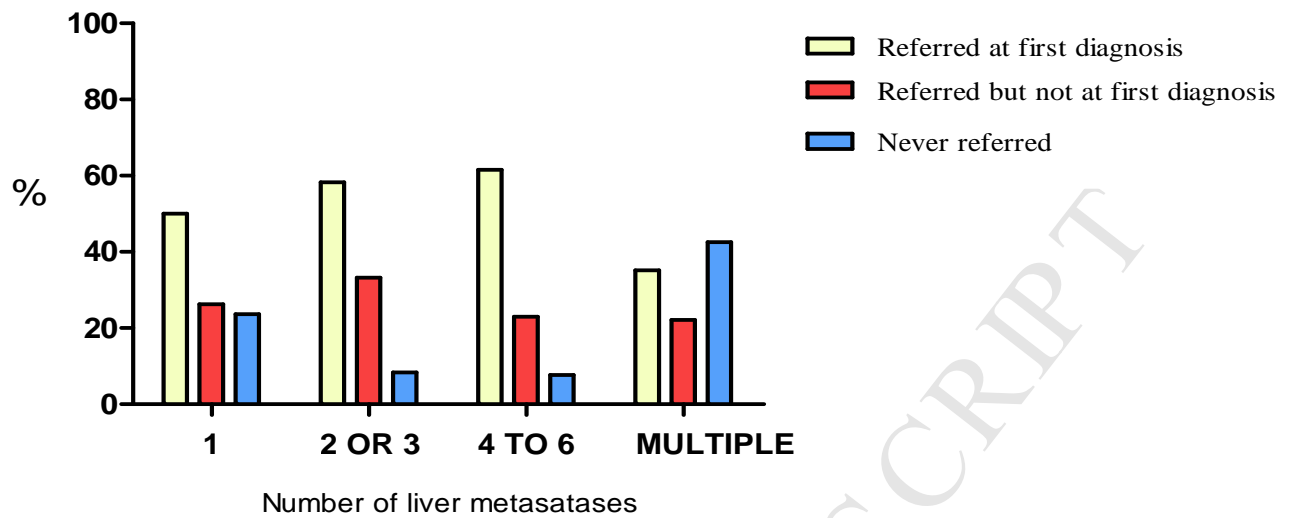


Figure 3. Percentage of patients that presented with 1, 2-3, 4-6 or multiple liver metastases per referral group. More than 40% of patients with a solitary liver metastasis were either not referred initially to the MDM or never referred.

	Referred at first diagnosis	Referred but not at first diagnosis	Never referred
<b>Surgery/RFA</b>	35/68 (51.5%)	18/38 (47.4%)	0/53 (0%)
<b>SIRT</b>	2/68 (2.9%)	0/38 (0%)	0/53 (0%)

Table 2. Patients who underwent surgery, RFA or SIRT per referral group. None of the patients that were not referred to the MDM underwent liver directed therapy. There was no difference in surgical/RFA practices between patients who were referred at



initial diagnosis and those that were subsequently referred. (RFA = radiofrequency ablation, SIRT = selective internal radiation therapy, MDM = multi-disciplinary).

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